European Journal of Immunology

Letter to the Editor

[DOI: 10.1002/eji.201948447]

Soluble IL-7 receptor alpha concentration in cord blood is linked to sex and maternal diabetes, but not with subsequent development of type 1 diabetes

Interleukin-7 (IL-7) interacts with the IL-7 receptor (IL-7Rα or CD127, and the common γ chain) to provide crucial survival and proliferation signals to T cells. Increased IL-7/IL-7R signaling has been associated with the activation and expansion of allo-reactive [1] and autoreactive T cells and the development of autoimmune diseases, including type 1 diabetes (T1D) [2]. IL-7/IL-7R signaling is regulated by two mechanisms. The circulating concentration of IL-7 depends on the uptake and consumption by T cells as IL-7 is produced by stromal cells at constant levels. As a consequence, lymphopenia is associated with increased circulating IL-7 and can lead to the expansion of autoreactive T-cell clones [3]. A second mechanism is the release of a soluble form of the IL-7R (sCD127). While the affinity of CD127 for IL-7 ($Kd = 10^{-8}$ M) is considerably lower than the CD127/common γ chain complex ($Kd = 10^{-11}$ M) on the T-cell surface [4], the circulating concentration of sCD127 is >10 000-fold higher than IL-7, suggesting that a significant fraction of IL-7 can be bound to sCD127. We [5] and others [6] found that sCD127 binding to IL-7 inhibits the biological activity of IL-7. Others, however, suggest that sCD127 potentiates IL-7 bioactivity by reducing excessive IL-7 consumption [7]. sCD127 is increased in T-cell activation. We had the opportunity to examine sCD127 concentrations in the first 3 months of life in children who were at risk for type 1 diabetes and asked whether there was evidence for early perinatal activation that might affect the likelihood of developing autoimmunity in these newborns.

Umbilical cord blood serum samples (CB) were collected from 237 (107 girls) newborns and peripheral blood samples were collected from 116 additional infants before age 3 months (66 girls). Samples were predominantly from children who had a mother with T1D ($n = 186$), father with T1D ($n = 99$), or both parents with T1D ($n = 9$) and who participated in prospective cohort studies at the Institute of Diabetes Research, Helmholtz Zentrum München. Children were prospectively followed for the development of islet autoantibodies and type 1 diabetes (median follow-up 17.9 years) with informed consent and ethics committee approval (Bayerische Landesärztekammer no. 95357 and Ludwig-Maximilians University no. 329/00). sCD127 serum concentration (ng/mL, median; interquartile range) was measured using a sandwich ELISA as described in the Supporting Information. A two-tailed Mann-Whitney *U* test was used for comparisons.

sCD127 serum concentration was increased in infants aged 14–90 days (median, 72.3; IQR, 41.8–98.6) as compared to samples taken at birth (median, 19.3; IQR 13.9–25.9, $p < 0.0001$) and at age 1–14 days (median, 12.3; IQR, 7.9–25.6; $p < 0.0001$) (Fig. 1). At birth, sCD127 was higher in females (median, 23.1; IQR, 7.4–31.5) than in males (median 15.9; IQR 11.6–21.6, $p = <0.0001$), in newborns with a gestational age <37 weeks (median, 36.7; IQR, 30.2–57.6) as compared to ≥37 weeks (median 18.9; IQR 13.8–24.6, $p < 0.0001$), and in newborns who had a mother with type 1 diabetes (median, 22.0; IQR, 17.4–27.9) as compared to children who did not have a mother with type 1 diabetes (median, 17.2; IQR, 11.6-23.3, $p < 0.0001$). No differences in cord blood sCD127 concentration were observed between children who developed T1D ($n = 42$; median, 20.3; IQR 12.7–32.7), or islet autoantibodies without T1D ($n = 32$; median, 19.3; IQR 15.0–25.0) as compared to children who remained islet autoantibody negative (median, 19.1; IQR 13.9–25.5). Sampling dates were evenly distributed throughout the year, and no relationship between sCD127 concentration and season was observed in a linear regression model including age and season.

Alterations of the circulating concentration of sCD127 have been involved in the pathogenesis of T1D. In this study, we report that sCD127 concentration in cord blood associates with protective factors such as sex and maternal T1D, but found no associations with future development of autoantibodies or T1D.

Circulating sCD127 concentration is very low at birth and in the first 2 weeks of life, but rapidly reached levels similar to those previously found in adults [5]. This might reflect the high cell cycle rate of cord blood cells as compared to adult PBMC [8], which is driven by the bioactivity of IL-7. IL-7 is indeed elevated in

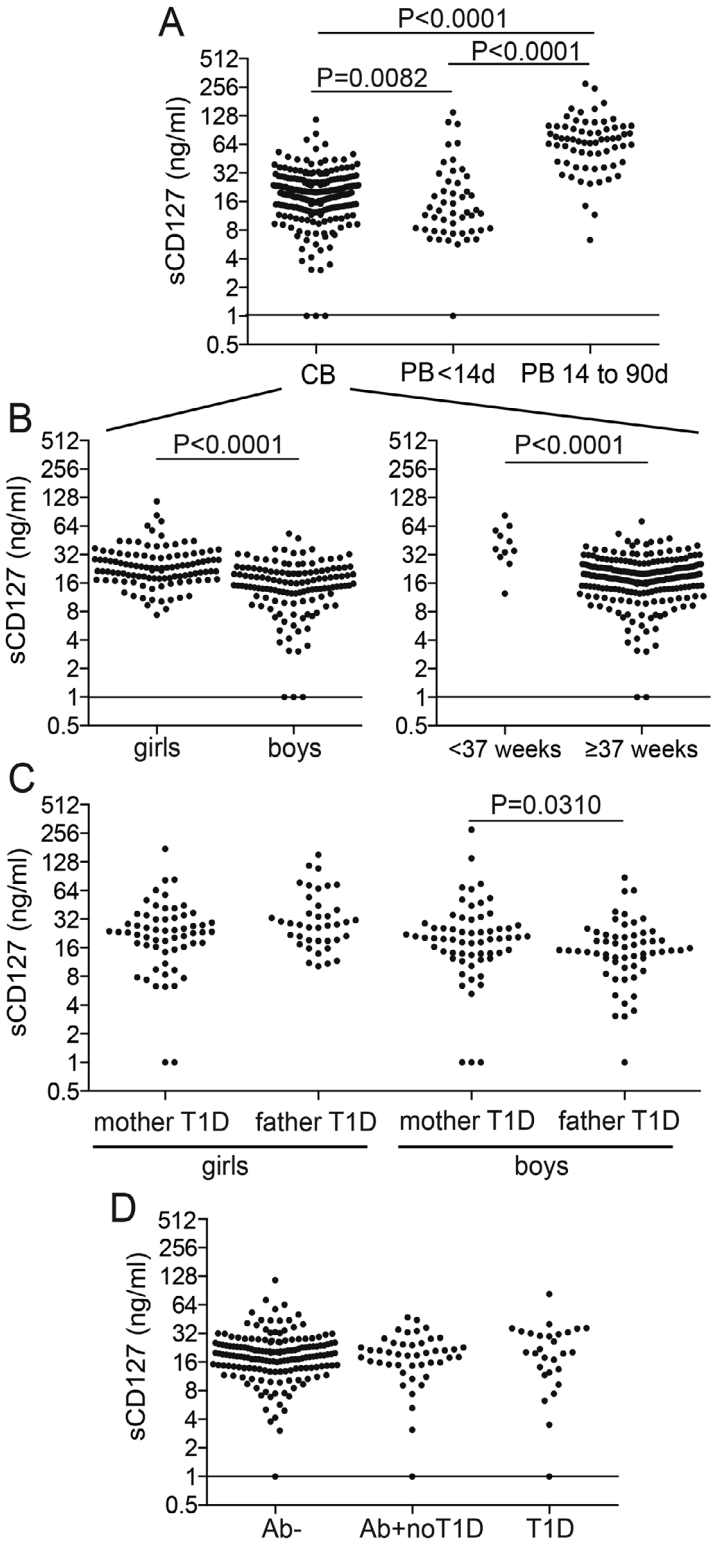

Figure 1. sCD127 concentration in sera from neonates and infants. (A) sCD127 concentrations in cord blood are shown in relation to sCD127 concentration in blood samples. All samples were obtained from different subjects with a familiar risk of developing T1D. (B) sCD127 concentrations in cord blood samples are shown in relation to the sex (left graph), gestational age (middle graph), and the diabetes status of the mother (left graph) of the subjects. (C) sCD127 concentrations are shown in cord blood in relation to the subsequent seroconversion or development of T1D. All data were measured using ELISA. *p* Values were calculated using the Mann–Whitney *U* test and are indicated on the top of each graph. *n* represents the number of patients.

cord blood samples and is also required to prevent apoptotic cell death of cord blood, but not adult T cells [9]. Assuming an inhibitory role of sCD127 on IL-7 biological activity, a low sCD127 concentration may have an important role in maintaining IL-7-mediated homeostatic proliferation and survival of T cells. Circulating concentration of sCD127 is also influenced by the release of the membrane-bound form during T-cell activation [5], suggesting that the contact of the immune system with environmental potential pathogens and the development of memory T cells in the first months of like could also contribute to the rapid increase of sCD127.

The T-cell repertoire in cord blood also includes T cells reactive to insulin and

GAD65 whose activation and differentiation is IL-7 dependent [9] and may explain how a higher concentration of sCD127 that reduce IL-7 biological activity associates with the protective factors of sex and maternal T1D. However, this is not associated with subsequent seroconversion and T1D manifestation, suggesting that other more relevant factors are determinant in the development of autoimmunity against beta cells.

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Acknowledgements: P.M. is supported by a Career Development Award from JDRF (5-CDA-2015-85-A-N).

Conflict of interest: The authors declare no commercial or financial conflict of interest.

Author contributions: P.M., E.B., and A.G.Z. conceived the study, designed experiments, and wrote the manuscript. D.V. performed experiments, acquired, and analyzed data.

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Keywords: autoimmunity • cord blood • newborns • soluble CD127 • type 1 diabetes

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The peer review history for this article is available at https://publons.com/publon/10.1002/eji.201948447

Received: 21/10/2019
Revised: 23/1/2020
Accepted: 12/2/2020
Accepted article online: 13/2/2020

